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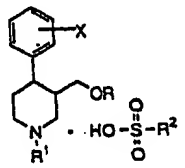

(I)

(57) Abstract

The invention relates to a compound, and pharmaceutically acceptable salts, having formula (I), wherein: R represents an alkyl or alkynyl group having 1–4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl; R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl; X represents hydrogen, alkyl having 1–4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy; R^2 represents: a C_1–C_{10} alkyl group; a phenyl group optionally substituted by one or more of the following groups: a C_1–C_{10} alkyl group, a halogen group, a nitro group, hydroxy group, and/or an alkoxy group.

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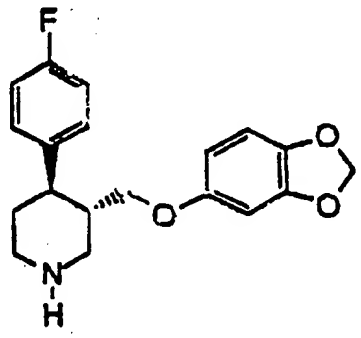
4-PHENYLPIPERIDINE COMPOUNDS

The present invention relates to a group of tri-substituted, 4-phenylpiperidines, to a process for preparing such compounds, to a medicament comprising such compounds, and to the use of such compounds for the manufacture of a medicament.

The compound paroxetine, trans-4-(4'-fluorophenyl)-3-(3',4'-methylene dioxyphenoxymethyl)piperidine having the formula below:



is known and has been used in medicaments for treating, amongst other ailments, depression.

Paroxetine has been used as a therapeutic agent in the form of a salt with pharmaceutically acceptable acids. The first clinical trials were conducted with the acetate salt.

A known useful salt of paroxetine is the hydrochloride. This salt is considered to be the active substance in several marketed pharmaceutical products, e.g. Paxil or Seroxat. A number of forms of paroxetine hydrochloride have been described:

- the anhydrous form in several crystalline modifications (PCT Appl. WO 96/24595);

- the hydrated form - a hemihydrate (EP 223403) and in the solvated forms.

The comparison of behaviour between anhydrous and hydrated form of paroxetine hydrochloride is described in the Intl. Journal of Pharmaceutics, 42, 135-143 (1988).

EP 223403 discloses paroxetine hydrochloride hemihydrate and pharmaceutical compositions based thereon.

Most of these known salts of paroxetine have unsuitable physico-chemical characteristics for ensuring safe and efficient handling during production thereof and formulation into final forms, since they are unstable (acetate, maleate) and possess undesirable hygroscopicity.

Furthermore their formation by crystallization from both aqueous or non-aqueous solvents is generally low-yielded and troublesome as they usually contain an undefined and unpredicted amount of bound solvent which is difficult to remove.

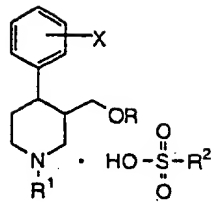
The crystalline paroxetine hydrochloride hemihydrate approaches these problems, but as stated in WO 95/16448, its limited photostability causes undesired colouration during classical wet tabletting procedure.

Moreover, crystalline paroxetine hydrochloride hemihydrate exhibits only limited solubility in water.

It has been generally suggested that where the aqueous solubility is low, for example less than 3 mg/ml, the dissolution rate at in vivo administration could be rate-limiting in the absorption process. The aqueous solubility of the paroxetine hemihydrate at room temperature exceeds this threshold by a relatively small margin.

An object of the present invention is to provide a compound with improved characteristics.

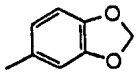
According to a first aspect, the present invention comprises a compound, and pharmaceutically acceptable salts, having the formula I:



- R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,
- R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,
- X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,
- R^2 represents:
  - a C1-C10 alkyl group,
  - a phenyl group optionally substituted by one or more of the following groups:
    - a C1-C10 alkyl group,
    - a halogen group,
    - a nitro group,
    - hydroxy group,
    - and/or an alkoxy group.

The inventors have found that these compounds exhibit good stability and very high solubility. This yields the advantage that high concentrations of the compound are obtainable in small volumes.

The R group is preferably the 3,4 methylenedioxyphenyl group of the formula:

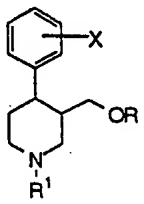


The X group is preferably a fluorine group attached to position 4 in the phenyl ring.

The R^2 group preferably represents a C1-C4 alkyl group, and most preferably represents a C1-C2 alkyl group in order to provide an optimum solubility.

The compounds can have a solubility at about 20 °C of at least about 10 mg/ml water, preferably having a solubility in water of at least 100, for example 500 and most preferably of at least 1000 mg/ml water.

According to a second aspect of the present invention, there is provided a process for preparing a compound as above, comprising the steps of mixing together a 4 phenylpiperidine compound, a salt and/or a base thereof having the formula II:



wherein:

- R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino,

methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,

- R_1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,
- X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy, .

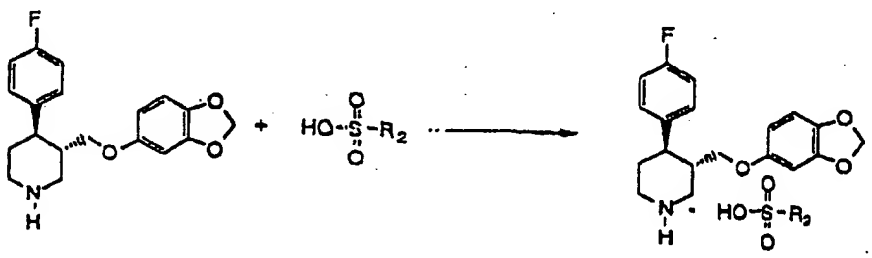
with a sulfonic acid of the general formula R_2-SO_3H, wherein R_2 represents:

- a C1-C10 alkyl group,
- a phenyl group optionally substituted by one or more of the following groups:
  - a C1-C10 alkyl group,
  - a halogen group,
  - a nitro group,
  - a hydroxy group, and/or
  - an alkoxy group,

to form a solution, followed by separating the compound formed from this solution.

The compounds of the invention can be prepared from the free base of the 4 phenylpiperidine, having the formula II, this preferably being paroxetine, by treatment with a sulfonic acid as defined above in a suitable solvent to form a solution of the desired acid addition salt, whereafter this is precipitated out of the solution.

The equation for paroxetine free base and sulfonic acids is as follows:

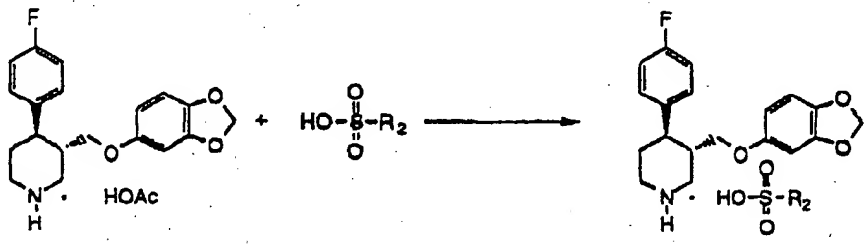


The forming of a solution may preferably proceed at temperatures from about 0 °C to the boiling point of the solvent.

Optionally, the solution may be purified by treatment of activated charcoal, silica gel, kieselguhr or other suitable materials.

Alternatively, the solution of a salt of the invention can be formed by dissolution of a salt of 4 phenyl piperidine having the formula II with an organic sulfonic acid.

For example the compounds of the invention may be prepared from a paroxetine C1-C5 carboxylate, such as the acetate, by addition of corresponding organic sulfonic acid to the solution of the said carboxylate, as follows:

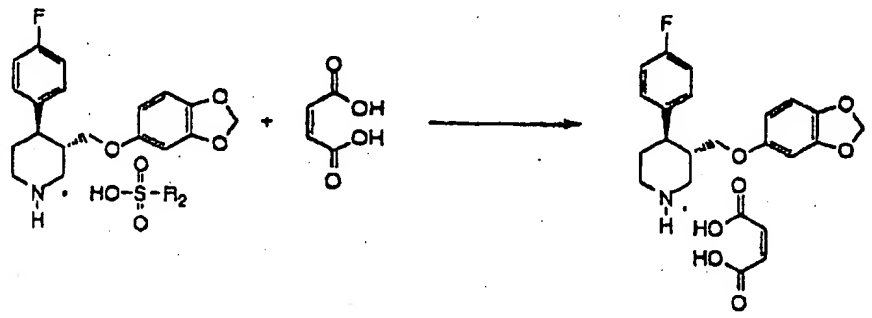


According to a third aspect of the present invention, there is provided a compound obtainable by this process.

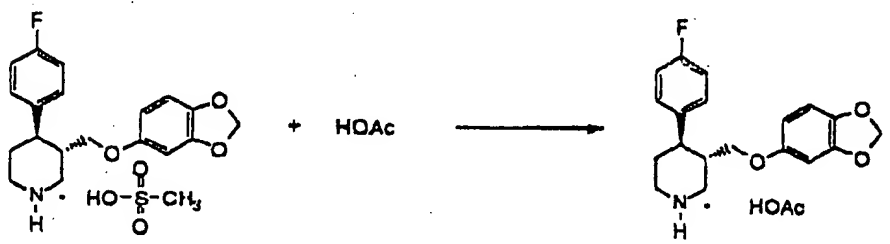
According to a fourth aspect of the present invention there is provided the above compound for use as a medicament and, according to a fifth aspect, a medicament comprising this compound, and to the use thereof for treating depressions, obsessive compulsive disorders, panic disorders, bulimia, anorexia, pain, obesity, senile demential, migraine, anorexia, social phobia, depressions arising from pre-menstrual tension.

According to a sixth aspect of the present invention, there is provided the use of a compound of the

invention as a reagent in further syntheses. More specifically, the compounds of the present invention can be used as a start reagent for forming further acid addition salts, for example for providing further paroxetine acid addition salts, by reacting with a suitable reagent, i.e. with a corresponding acid. For example, the formation of paroxetine maleate according to the present invention proceeds by the following equation:



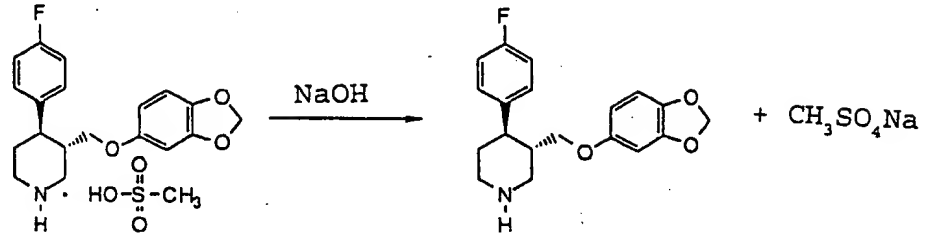
and the formation of paroxetine acetate proceeds as follows:



This is an advantageous route, since by using the substantially pure sulfonic acid salts according to the present invention as a start reagent, the preparation of a further salt, as above, results in this further salt having a high purity. The inventors have shown that such salts have a surprisingly high purity.

Similarly, the compounds of the present invention can react with a base, such as an inorganic and/or an organic base, to form (liberate) free bases of the corresponding compounds. As exemplified on

paroxetine, the reaction proceeds according to the equation:



The free bases liberated from the compounds of the present invention have surprisingly higher purity than if prepared by known methods which is especially important in case of their use for production of pharmaceuticals.

Accordingly, the new compounds of the first aspect of the invention can also form hydrates and/or solvates by a contact with a corresponding reaction partner, i.e. with water and/or with a solvent. Examples of such further salts, hydrates and solvates, for example these of paroxetine, are the:

hydrochloride	oxalate	dihydrate
hydrobromide	succinate	trihydrate
hydroiodide	tartrate	hexahydrate
acetate	citrate	methanolate
propionate	embonate	ethanolate
maleate	hemihydrate	
fumarate	hydrate	

The inventors have shown that such salts have a surprisingly high purity.

Examples of bases which can be employed in the preparation of the free bases are: sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonium hydroxide, sodium carbonate, methylamine, dimethylamine, triethylamine, pyridine and such like.

Since the compounds according to the present invention exhibit high solubility, they can be dosed, for

example injected, in a high concentration, low volume solution, this method of dosing being particularly advantageous with certain patients, such as manic depressives and such like, i.e. patients who are unable or unwilling to swallow medicine.

The compounds of the present invention can be formulated into various types of pharmaceutical compositions for treatment of humans and animals. Pharmaceutical compositions according to the present invention comprise a compound of the invention alone or together with a pharmaceutically acceptable carrier or diluent. The preferred formulations are those for oral administration (tablets, capsules) but formulations for parenteral or topical administration are also within the scope of the invention. The high water solubility of the compounds of the invention enables high dissolution rates in solid dosage forms based on the compounds of the invention to be obtained, during the in vitro release as well as good bioavailability after peroral application in vivo.

The tablets containing compounds of the present invention can be prepared both by tabletting procedure in which water is present (e.g. aqueous granulation) as well as by tabletting processing it which water is absent (direct compression, dry granulation) and may be coated by any suitable means of coating.

The present invention will now be further elucidated by way of the following examples and results.

EXPERIMENTAL

A seeding crystal of paroxetine methane sulfonate was made as follows:

2.7 g (8.2 mmol) of paroxetine was dissolved in 15 ml of hot ethanol.

1.0 g (10.4 mmol) of methanesulfonic acid in 15 ml of ethanol was added and the mixture was cooled to room temperature. When the mixture had

reached room temperature the mixture was put in the freezer at -20 °C overnight. No crystal line compound was obtained.
The mixture was evaporated to dryness leaving an oil.
After 1 month at room temperature a waxy solid was obtained. Part of this solid was taken apart and the rest was dissolved in
10 ml of EtOAc. The waxy crystals were added and the mixture was put in the freezer at -20 °C overnight. A white crystalline product was precipitated. After filtration and drying in a vacuumoven
2.5 g (5.9 mmol) of paroxetine methane sulfonate was obtained.
Yield 72%
This seeding crystal was subsequently used in following examples 1 and 3.

Examples

Example 1

Paroxetine methane sulfonate from paroxetine

To a solution of 43.5 g (132 mmol) of paroxetine, prepared by the procedure disclosed in US 4007196,
12.7 g (132 mmol) of methane sulfonic acid was added to
150 ml of boiling ethyl acetate. The mixture was left at room temperature for 2 hours. Subsequently the mixture was placed overnight at -20 °C, with a seeding crystal. The obtained solid was filtered off and washed with
50 ml of ether. The obtained white solid was dried overnight in a vacuumoven.
47.1 g (111 mmol) of product
Yield 99.5%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 98% (HPLC).

Example 2

Paroxetine benzene sulfonate from paroxetine

3.8 g (11.5 mmol) of paroxetine was dissolved in 10 ml of hot ethylacetate. 1.82 g (11.5 mmol) of anhydrous benzenesulfonic acid was added. The mixture was left at room temperature for 2 h. The mixture was evaporated to dryness and dissolved in dichloromethane, and evaporated again to dryness leaving an oil. This oil was solidified through high vacuum (0.1 mmHg) evaporation leaving 5.0 g (1.3 mmol) of an off white solid. To this solid was added 5 ml of acetone and the suspension was stirred for 5 minutes during which a white suspension was obtained. The solid was filtered off and dried under vacuum. 4.8 g (9.9 mmol) of product was obtained. Yield 85%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 3

Paroxetine p-toluene sulfonate from paroxetine

5.0 g (15 mmol) of paroxetine was dissolved in 25 ml of hot ethylacetate. 2.9 g (15 mmol) of p-toluenesulfonic acid was added. The mixture was left at room temperature for 2 h and subsequently put in the freezer, with a seeding crystal, for 14 h. The solid was filtered off and washed once with

10 ml of n-hexane. The obtained white solid was dried overnight in a vacuumoven.
4.8 g (10 mmol) of a white solid was obtained.
Yield 67%
Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 4

Paroxetine p-chlorobenzene sulfonate from paroxetine

1.1 g (3.3 mmol) of paroxetine was dissolved in
3 ml of hot ethylacetate.
0.76 g (3.3 mmol) of 90% p-chlorobenzenesulfonic acid was added. The mixture was left at room temperature for 1 h and washed with
5 ml of water. The organic layer was dried with Na_2SO_4, filtered and evaporated to dryness leaving
1.5 g (2.9 mmol) of an off white solid.
Yield 88%
Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 5

Paroxetine maleate from paroxetine methane sulfonate

1.0 g (2.4 mmol) of paroxetine methane sulfonate in
5 ml of hot water. To this solution was added
0.32 g (2.8 mmol) of maleic acid. The mixture was placed at 4 °C overnight after which a solid with a yellow oil was precipitated on the bottom of the flask. The solid/oil was filtered off and washed 3 times with
10 ml of ether and dried in a vacuumoven.
0.8 g (2.0 mmol) off white crystals were obtained
Yield 85%

The purity of the compound obtained was 99.5% (HPLC).

Example 6

Paroxetine acetate from paroxetine methane sulfonate

1.0 g (2.4 mmol) of paroxetine methane sulfonate in 5 ml of hot iso-propanol. To this solution was added 0.2 g (3.2 mmol) of acetic acid. The mixture was placed at 4 °C overnight after which a solid was precipitated. The solid was filtered off and washed 3 times with 10 ml of ether and dried in a vacuumoven. 0.5 g (1.3 mmol) off white crystals were obtained

Yield 54%

The purity of the compound obtained was 99.5% (HPLC).

Example 7

Paroxetine free base from paroxetine methane sulfonate

10.0 g (24.0 mmol) of paroxetine methane sulfonate in 150 ml of water and 200 ml of ethyl acetate. To this was added 12.4 g (31 mmol) of an aqueous 10 wt% NaOH solution and the suspension was stirred for 15 minutes. The layers were separated and the aqueous layer was extracted once with 50 ml of ethyl acetate. The combined organic layers are washed once with 100 ml of water and dried over Na_2SO_4. The Na_2SO_4 was filtered off and washed once with 50 ml of ethyl acetate. The ethyl acetate was evaporated off, leaving 7.5 g (22.8 mmol) of an oily product.

Yield 95%

The purity of the compound obtained was 99.5% (HPLC).

A number of the compounds obtained were analysed, the results being shown in tables 1-5 below:

Table 1
Characterization of salts of paroxetine with certain organic sulfonic acids $R\text{-}SO_3H$

R = CH_3 - (paroxetine methane sulfonate):
m.p.: 142°-144°C.
DSC curve (closed pan, 10°C/min): onset 145.8°C, 79.0 J/g.
IR spectrum (KBr, in cm^{-1}): 531, 546, 777, 838, 931, 962, 1038, 1100, 1169, 1208, 1469, 1500, 1515, 1615, 2577, 2869, 2900, 3023.
1H-NMR (ppm): 1.99 (br d, H_{5eq}, 1H); 2.27 (ddd, H_{5ax}, 1H); 2.48-2.65 (m, H_3, 1H); 2.82-2.92 (m, H_4 , CH_3, 4H); 2.95-3.20 (m, H_{2ax}, H_{6ax}, 2H); 3.47 (dd , H_7, 1H); 3.58-3.74 (m, H_{2eq}, H_{6eq}, H_7, 3H); 5.88 (s, $H_{7''}$, 2H); 6.10 (dd, $H_{6''}$, 1H); 6.33 (d, $H_{2''}$, 1H); 6.61 (d, $H_{5''}$, 1H); 7.09 (dd, $H_{3'}$, $H_{5'}$, 2H); 7.22 (dd , $H_{2'}$, $H_{6'}$, 2H); 8.85 (br d, NH_{eq}, 1H); 9.11 (br d, NH_{ax}, 1H).
13C-NMR (ppm): 30.0 (s, C_5); 39.3 (s, C_3); 39.5 (s, C_4); 41.7 (s, SC); 44.6 (s, C_6); 46.8 (s, C_2); 67.4 (s, C_7); 97.8 (s, $C_{2''}$); 101.2 (s, $C_{7''}$); 105.4 (s, $C_{6''}$); 107.8 (s, $C_{5''}$); 115.8 (d, $C_{3'}$, $C_{5'}$); 128.4 (s, $C_{6'}$, $C_{2'}$); 137.1 (s, $C_{4''}$); 142.0 (s, $C_{1'}$); 148.2 (s, $C_{3''}$); 153.7 (s, $C_{1''}$); 161.9 (d, $C_{4'}$).

R = *C_6H_5- (paroxetine benzene sulfonate)*:
m.p.: 55°-60°C.
IR spectrum (KBr, in cm^{-1}): 530, 564, 614, 689, 728, 764, 828, 929, 993, 1007, 1029, 1121, 1179, 1229, 1443, 1471, 1486, 1514, 1600, 1628, 2557, 2842, 3029.
1H-NMR (ppm): 1.90 (br d, H_{5eq}, 1H); 2.10-2.28 (m , H_{5ax}, 1H); 2.38-2.52 (m, H_3, 1H); 2.82 (ddd, H_4, 1H); 3.02-3.18 (m, H_{2ax}, H_{6ax}, 2H); 3.37 (dd, H_7, 1H); 3.48 (d, H_7, 1H); 3.60-3.82 (m, H_{2eq}, H_{6eq}, 2H); 5.87 (s, $H_{7''}$, 2H); 6.06 (dd, $H_{6''}$, 1H); 6.29 (d, $H_{2''}$, 1H); 6.60 (d, $H_{5''}$, 1H); 6.90 (dd, $H_{3'}$, $H_{5'}$, 2H); 7.04 (dd, $H_{2'}$, $H_{6'}$, 2H); 7.40 (d, ArH, 3H); 7.94 (d, $SArH$, 2H); 8.81 (br d, NH_{eq}, 1H); 9.04 (br d, NH_{ax} 1H).
13C-NMR (ppm): 29.9 (s, C_5); 39.2 (s, C_3); 41.5 (s, C_4); 44.8 (s, C_6); 47.0 (s, C_2); 67.3 (s, C_7); 97.9 (s, $C_{2''}$); 101.2 (s, $C_{7''}$); 105.5 (s, $C_{6''}$) 107.8 (s, $C_{5''}$); 115.7 (d, $C_{3'}$, $C_{5'}$); 125.9 (s, C_b); 128.6 (s, C_d); 128.8 (s, $C_{6'}$, $C_{2'}$); 130.6 (s, $C_{c\pi}$); 137.1 (s, $C_{4''}$); 141.9 (s, $C_{1'}$); 144.1 (s, C_a); 148.2 (s, $C_{3''}$); 153.7 (s, $C_{1''}$); 161.8 (s, $C_{4'}$).

R = *$p\text{-}CH_3C_6H_4$ (paroxetine p-toluene sulfonate)*:
m.p.: 148°-150°C.
DSC curve (closed pan, 10°C/min): onset 151.6°C, 71.6 J/g.
IR spectrum (KBr, in cm^{-1}): 529, 557, 671, 771, 800, 814, 921, 936, 1000, 1029, 1100, 1157, 1186, 1229, 1471, 1486, 1507, 1600, 2557, 2829, 3029.
1H-NMR (ppm): 1.89 (br d, H_{5eq}, 1H); 2.10-2.50 (m, H_{5ax}, H_3, CH_3, 5H); 2.82 (ddd, H_4, 1H); 2.97-3.18 (m, H_{2ax}, H_{6ax}, 2H); 3.36 (dd, H_7, 1H); 3.48 (dd, H_7, 1H); 3.52-3.77 (m, H_{2eq}, H_{6eq}, 2H); 5.87 (s, $H_{7''}$, 2H); 6.06 (dd, $H_{6''}$,1H); 6.28

Table 1 (continued) Characterization of salts of paroxetine with certain organic sulfonic acids R-SO_3H
(d, $H_{2''}$, 1H); 6.59 (d, $H_{5''}$, 1H); 6.90 (dd, $H_{3'}$, $H_{5'}$, 2H); 7.05 (dd, $H_{2'}$, $H_{6'}$, 2H); 7.24 (d, CH_3ArH, 2H); 7.83 (d, $SArH$, 2H); 8.91 (br d, NH_{eq}, 1H); 9.17 (br d, NH_{ax}, 1H). 13C-NMR (ppm): 21.3 (s, C_e); 29.9 (s, C_5); 39.2 (s, C_3); 41.5 (s, C_4); 44.7 (s, C_6); 46.9 (s, C_2); 67.3 (s, C_7); 97.8 (s, $C_{2''}$); 101.1 (s, $C_{7''}$); 105.5 (s, $C_{6''}$); 107.8 (s, $C_{5''}$); 115.6 (d, $C_{3'}$, $C_{5'}$); 125.8 (s, C_b); 129.0 (s, $C_{6'}$, $C_{2'}$); 129.1 (s, C_c); 137.2 (s, $C_{4''}$); 140.8 (s, C_d); 141.5 (s, C_a); 141.9 (s, $C_{1'}$); 148.2 (s, $C_{3''}$); 153.8 (s, $C_{1''}$); 161.8 (d, $C_{4'}$).
R = *p-ClC_6H_4 (paroxetine p-chlorobenzene sulfonate)*; m.p.: 75°-80°C. IR spectrum (KBr, in cm^{-1}): 486, 557, 643, 736, 821, 1000, 1029, 1086, 1114, 1186,1229, 1471, 1486, 1514, 1600, 1657, 2857, 3029. 1H-NMR (ppm): 1.91 (br d, H_{5eq}, 1H); 2.15 (ddd, H_{5ax}, 1H); 2.37-2.52 (m, H_3, 1H); 2.81 (ddd, H_4, 1H); 2.93-3.21 (m, H_{2ax}, H_{6ax}, 2H); 3.37 (dd, H_7, 1H); 3.49 (d, H_7, 1H); 3.61-3.81 (m, H_{2eq}, H_{6eq}, 2H); 5.88 (s, $H_{7''}$, 2H); 6.05 (dd, $H_{6''}$, 1H); 6.27 (d, $H_{2''}$, 1H); 6.59 (d, $H_{5''}$, 1H); 6.91 (dd, $H_{3'}$, $H_{5'}$, 2H); 7.03 (dd, $H_{2'}$, $H_{6'}$, 2H); 7.39 (d, $ClArH$, 2H); 7.86 (d, $SArH$, 2H); 8.78 (br d, NH_{eq}, 1H); 9.02 (br d, NH_{ax}, 1H). 13C-NMR (ppm): 30.0 (s, C_5); 39.3 (s, C_3); 41.5 (s, C_4); 44.9 (s, C_6); 47.1 (s, C_2); 67.3 (s, C_7); 97.9 (s, $C_{2''}$); 101.2 (s, $C_{7''}$); 105.5 (s, $C_{6''}$); 107.9 (s, $C_{5''}$); 115.8 (d, $C_{3'}$, $C_{5'}$); 127.6 (s, C_b); 128.8 (s, $C_{6'}$, $C_{2'}$); 132.0 (s, C_d); 137.0 (s, C_c); 137.2 (s, $C_{4''}$); 141.8 (s, $C_{1'}$); 142.0 (s, C_a); 148.2 (s, $C_{3''}$); 153.6 (s, $C_{1''}$); 161.8 (d, $C_{4'}$).

The compounds of the invention are crystalline, with defined melting points, DSC curves and IR spectra. It cannot be excluded that, under different conditions of their formation and under specific conditions, they could exist also in other crystalline or polymorph modifications which may differ from those as described herein. The compounds of the invention are also generally very stable and non-hygroscopic.

It should be understood that the present invention comprising acid addition salts with organic sulfonic acids are substantially free of the bound organic solvent. Preferably, the amount of bound organic solvent should be less than 2.0% (w/w) as calculated on the anhydrous basis. They nevertheless may contain crystallization water and also unbound water, that is to say water which is other than water of crystallization.

In the following tables 2 and 3, examples of results of hygroscopicity tests and stability tests (in comparison with known salts of paroxetine) are presented.

Table 2
Hygroscopicity of certain salts of paroxetine (40°C, 75 % rel.hum).

water content (in %) at	t = 0	t = 4 weeks
methane sulfonate	0.35	+ 0.04
p-toluene sulfonate	0.70	< 0.02
hydrochloride	-	+ 2.5

Table 3
Solubility of paroxetine salts in water (in mg/ml)

	20°C	50°C
methane sulfonate	> 1000 / 10 min	1300
p-toluene sulfonate	> 1000	> 1000
hydrochloride hemihydrate	4.9	12.6
hydrochloride anhydrate	8.2	24.2

Table 4
Stability of paroxetine salts by HPLC (total amount of degradation in %).

	degradation 20°C	80°C
methane sulfonate	not observed	< 0.2 %, 3 months
p-toluene sulfonate	not observed	< 0.2 %, 3 months
maleate	0.2 %, 12 months	> 50 %, 5 days

Table 5
Solubility of salts of paroxetine in nonaqueous solvents (in mg/ml)

		methane sulfonate	p-toluene sulfonate
Ethanol	20°C	36	50
	78°C	250	> 500
2-Propanol	20°C	7	14
	82°C	330	> 500
Acetone	20°C	5	16
	56°C	37	125
Ethyl acetate	20°C	2	22
	77°C	25	> 500
n-Hexane	20°C	< 0.05	< 0.05
	69°C	0.05	< 0.05

Examples of analytical data of the paroxetine salts and the free base prepared in Examples 5 to 7 are given in Table 6.

Table 6
Characterization of salts / free base of paroxetine

paroxetine maleate: m.p.: 128-130°C. 1H-NMR (ppm): 1.65-2.00 (m, H_{5eq}, H_{5ax}, 2H); 2.00-2.50 (m, H_3, 1H); 2.55-3.15 (m, H_{2ax}, H_{6ax}, H_4, 3H); 3.15-3.75 (m, H_{2eq}, H_{6eq}, H_7, 3H); 5.67 (s, $H_{7''}$, 2H); 5.97 (s, H_a, 1H); 6.12 (dd, $H_{6''}$, 1H); 6.42 (d, $H_{2''}$, 1H); 6.67 (d, $H_{5''}$, 1H); 6.95-7.35 (m, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$, 4H).
paroxetine acetate: m.p.: 123-125°C. 1H-NMR (ppm): 1.70-2.00 (m, H_{5eq}, H_{5ax}, 2H); 1.97 (s, H_a, 3H); 2.05-2.50 (m, H_3, 1H); 2.50-3.00 (m, H_4, H_{2ax}, H_{6ax}, 3H); 3.05-3.75 (m, H_{2eq}, H_{6eq}, H_7, 3H); 6.05 (s, $H_{7''}$, 2H); 6.28 (dd, $H_{6''}$, 1H); 6.58 (d, $H_{2''}$, 1H); 6.65 (d, $H_{5''}$, 1H); 7.10-7.50 (m, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$, 4H).
paroxetine: 1H-NMR (ppm): 1.60-2.00 (m, H_{5ax}, H_{5eq}, 2H); 2.00-2.35 (m, H_3, 1H); 2.40-2.95 (m, H_4, H_{2ax}, H_{6ax}, 3H); 3.15-3.70 (m, H_{2eq}, H_{6eq}, H_7, 2H); 5.67 (s, $H_{7''}$, 2H); 6.11 (dd, $H_{6''}$,1H); 6.43 (d, $H_{2''}$, 1H); 6.62 (d, $H_{5''}$, 1H); 6.80-7.35 (m, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$, 4H).

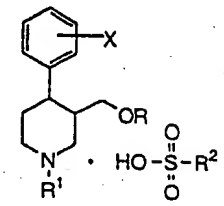
It will be clear that the invention is not limited to the above description, but is rather determined by the following claims.

Reference

- Psychopharmacology, 57, 151-153 (1978)]; ibid. 68, 229-233 (1980), European Journal of Pharmacology, 47, 351-358 (1978)]; in USP 4007196, the preparation of paroxetine maleate is reported.

CLAIMS

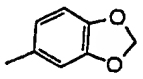
1. A compound, and pharmaceutically acceptable salts, having the formula I:



wherein:

- R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,
- R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,
- X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,
- R^2 represents:
    - a C1-C10 alkyl group,
    - a phenyl group optionally substituted by one or more of the following groups:
        - a C1-C10 alkyl group,
        - a halogen group,
        - a nitro group,
        - hydroxy group,
        - and/or an alkoxy group.

2. Compound according to claim 1, wherein the R group is the 3,4 methylene dioxy phenyl group of the formula:



3. Compound according to claim 1 or 2, wherein the X group is preferably a fluorine group attached to position 4 in the phenyl ring.

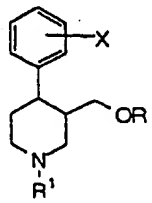
4. Compound according to claim 1-3, wherein the R^2 group represents a C1-C4 alkyl group.

5. Compound according to claims 1-4, wherein the R^2 group is a C1-C2 alkyl group.

6. Compound according to any of the previous claims, having a solubility at about 20 °C of at least about 10 mg per ml water.

7. Compound according to claim 6, having a solubility in water of at least 100, preferably at least 500 and most preferably of at least 1000 mg per ml.

8. Process for preparing a compound according to any of the previous claims, comprising the steps of mixing together a compound, a salt and/or a base thereof, having the formula II:



wherein:

- R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,
- R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,
- X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy, with a sulfonic acid of the general formula R^2-SO_3H, wherein R^2 represents:
  - a C1-C10 alkyl group,
  - a phenyl group optionally substituted by one or more of the following groups:
    - a C1-C10 alkyl group,
    - a halogen group,
    - a nitro group,
    - hydroxy group,
    - and/or an alkoxy group,

to form a solution, whereafter the solid formed may be separated out.

9. Compound according to any of the claims 1-7 obtainable by the process according to claim 8.

10. Compound according to any of the claims 1-7 and 9, for use as a medicament.

11. Medicament comprising a compound according to any of the claims 1-7, 9, 10 and pharmaceutically acceptable carriers/diluents.

12. Use of a compound according to any of the claims 1-7, 9, 10 for preparing a medicament.

13. Use of a compound according to any of the claims 1-7 for the manufacture of a medicament for treating depressions, obsessive compulsive disorders, panic disorders, bulimia, anorexia, pain, obesity, senile demential, migraine, anorexia, social phobia, depressions arising from pre-menstrual tension.

14. Use of a compound according to any of the claims 1-7, 9, 10 as a reagent in further syntheses.

15. Process for providing a salt ion or solvate, comprising the steps of mixing together a compound according to any of the claims 1-7, 9 and 10 with a reagent selected from the group consisting essentially of:

hydrochloric acid	citric acid
hydrobromic acid	embonic acid/pamoic acid
hydriodic acid	sulfuric acid
acetic acid	water
propionic acid	methanol
maleic acid	ethanol
fumaric acid	
oxalic acid	
succinic acid	
tartaric acid	

16. Salt obtainable by the process according to claim 15.

17. Salt according to claim 16, having a purity of at least 90 wt%, preferably at least 95 wt% and most preferably at least 98%.

18. Paroxetine maleate having a purity of at least 98%.

19. Paroxetine acetate having a purity of at least 98%.

20. Process for providing a free base comprising the step of mixing together a compound according to any of the claims 1-7, 9, 10 with an organic and/or inorganic base.

21. Process according to claim 20, wherein the base is selected from the group consisting essentially of: sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonium hydroxide, sodium carbonate, methylamine, dimethylamine, triethylamine, pyridine.

22. A free base obtainable by the process according to claims 20 or 21, said free base having a purity of at least 95% and most preferably at least 98%.

23. Paroxetine free base according to claim 22, having a purity of at least 98%.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/NL 97/00328

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D405/12 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BUXTON P C ET AL: "Solid-state forms of paroxetine hydrochloride" INT. J. PHARM. (IJPHDE,03785173);88; VOL.42 (1-3); PP.135-43, BEECHAM PHARM.;BIOSCI. RES. CENT.; EPSOM SURREY; KT18 5XQ; UK (GB), XP000572028 cited in the application see the whole document ---	1-13
A	WO 96 24595 A (SMITHKLINE BEECHAM PLC) 15 August 1996 cited in the application see the whole document ---	1-13
A	EP 0 223 403 A (BEECHAM GROUP PLC) 27 May 1987 cited in the application see the whole document ---	1-13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
5 February 1998	15. 05. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

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INTERNATIONAL SEARCH REPORT

Internat' ' Application No
PCT/NL 97/00328

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 269 303 A (A/S FERROSAN) 1 June 1988 see claims 1,6,7 ---	1-13
A	EP 0 152 273 A (A/S FERROSAN) 21 August 1985 see the whole document ---	1-13
A	EP 0 190 496 A (BEECHAM GROUP PLC) 13 August 1986 see page 3, last paragraph -----	1-13

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NL 97/ 00328

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see separate sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

claims 1 - 13

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

1. Claims: 1-13

   Compounds of the formula I, their preparation, and their use as a medicament

2. Claim : 14

   Use of the compound of claim 1 as a reagent in further synthesis

3. Claims: 15-19

   Process for the preparation of a salt of the compound of claim 1, the salt obtainable by the process, and certain specific salts of paroxetine.

4. Claims: 20-23

   process for providing a free base using the compound fo claim 1, the free base per se, and the known paroxetine free base with a purity of at least 98%.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna l Application No
PCT/NL 97/00328

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INTERNATIONAL SEARCH REPORT

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Internal Application No
PCT/NL 97/00328

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat Application No
PCT/NL 97/00328

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